SIMULATED SPACE RADIATION: MURINE SKELETAL RESPONSES DURING RECOVERY AND WITH MECHANICAL STIMULATION

Yasaman Shirazi-Fard[1], Josergio Zaragoza[1], Ann-Sofie Schreurs[1], Tiffany Truong[1], Candice Tahimic[1], Joshua S. Alwood[1], Alesha B. Castillo[2], and R. K. Globus[1]
[1]NASA Ames Research Center, Moffett Field, CA, [2]New York University, New York, NY

Simulated space radiation at doses similar to those of solar particle events or a round-trip sojourn to Mars (1-2Gy) may cause skeletal tissue degradation and deplete stem/progenitor cell pools throughout the body. We hypothesized that simulated space radiation (SSR) causes late, time-dependent deficits in bone structure and bone cell function reflected by changes in gene expression in response to anabolic stimuli. We used a unique sequential dual ion exposure (proton and iron) for SSR to investigate time-dependence of responses in gene expression, cell function, and microarchitecture with respect to radiation and an anabolic stimulus of axial loading (AL).

Male 16-wk C57BL6/J mice (n=120 total) were exposed to 0Gy (Sham, n=10), ^{56}Fe (2Gy, positive control dose, n=10), or sequential ions for SSR (1Gy ^{1}H/^{56}Fe/^{1}H, n=10) by total body irradiation (IR), and the tissues were harvested 2 or 6 mo. later. Further, to assess the response to anabolic stimuli, we subjected additional Sham-AL (n=15) and SSR-AL (n=15) groups to rest-inserted tibial axial loading (AL) starting at 1 and 5 months post-IR (-9N, 60 cycles/day, 3 days/wk, 4 wks). Exposure to ^{56}Fe caused a significant reduction in cancellous bone volume fraction (BV/TV) compared to Sham (-34%) and SSR (-20%) in the proximal tibia metaphysis at 2-months post-IR; however BV/TV for SSR group was not different than Sham. Both ^{56}Fe and SSR caused significant reduction in trabecular number (Tb.N) compared to Sham (-33% and -16%, respectively). Further, Tb.N for ^{56}Fe (2Gy) was significantly lower than SSR (-21%). *Ex vivo* culture of marrow cells to assess growth and differentiation of osteoblast lineage cells 6 months post-IR showed that both ^{56}Fe and SSR exposures significantly impaired colony formation compared to Sham (-66% and -54%, respectively), as well as nodule mineralization (-90% and -51%, respectively). Two-way analysis of variance showed that both mechanical loading and radiation reduced BV/TV, mechanical loading reduced trabecular thickness (Tb.Th), and radiation reduced Tb.N, at both time points. To assess acute response to mechanical stimuli, samples were harvested from a subset of Sham-AL (n=5) and SSR-AL (n=5) to measure changes in gene expression levels. Preliminary results indicate that axial loading increased expression of the antioxidant response gene *Nfe2l2* and the osteoprogenitor-associated marker *Runx2* in the bone marrow cells, and there was an interaction effect between axial loading and radiation at 2-months post-IR. Additional analyses of gene expression levels in the mineralized tissue are in progress.

Results indicate that SSR caused persistent impairment of osteoblast colony formation and nodule mineralization 6-mo post-IR. Contrary to our hypothesis, simulated space radiation did not impair the ability of cancellous bone to respond to a mechanical anabolic stimulus, consistent with our previous findings [1]. Hence, compressive loading may be a potential countermeasure against spaceflight-induced bone loss.

REFERENCES

[1] Shirazi-Fard Y., Alwood J.S., Schreurs A.S., Castillo A.B., Globus R.K. (2015) *Bone* 81, 260-269.

ACKNOWLEDGMENT

This work is supported by the National Space Biomedical Research Institute through NCC 9-58, and Space Biology/NASA Space Biology Postdoctoral Fellowship awards.